

Chapter 29: Clinical Translation and Implementation Neuroscience for Novel Cognitive Interventions in Addiction Medicine

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1. Introduction

Recent advances in the neuroscience of drug addiction motivates questions concerning whether and how clinical practice may be based on or inspired by these new advances. In this chapter, we will provide a framework for summarizing novel, neuroscience-informed, cognitive interventions that are under investigation and/or in the process of translation to clinical practice. We will provide more specific information concerning our experience in developing a new integrative package of interventions inspired by this framework. At the end of the chapter, we will discuss the next steps in the clinical translation and implementation of neuroscience-based cognitive interventions.

2. Neuroscience-based Cognitive Interventions

Chronic and prolonged use of various substances (including alcohol) may change or induce damages in different brain regions and networks including subcortical (Nagel, Schweinsburg, Phan, & Tapert, 2005), frontal (Koester et al., 2012), orbitofrontal (Tanabe et al., 2009), cingulate, limbic and paralimbic cortices (Thompson et al., 2004). These identified structural alterations have been associated with several cognitive-related functional pathologies, which can be classified into two distinct but interacting categories: cognitive maladaptation (CM) and cognitive deficits (CD). Cognitive maladaptation is an umbrella term for any “neuroadaptation” resulting from extreme saliency of drug rewards. High sensitivity to short-term rewards and preference for processing drug related cues are some examples of cognitive maladaptation in substance users that could be potentially revised with cognitive modifications (e.g., attention bias modification) (Hamed Ekhtiari, Victor, & Paulus, 2017; Rezapour, Wurfel, Simblett, & Ekhtiari, 2017). In the second category, there is a varied profile of cognitive deficits experienced by substance users, thought to be caused by “neurotoxic effects” of drugs. These deficits have been described in a variety of domains, including learning and memory, attention and concentration, executive functioning, and visuospatial processing (Baldacchino, Tolomeo, Balfour, & Matthews, 2018). Cognitive rehabilitation may be a promising strategy for targeting these functions (Rezapour, Hatami, et al., 2017a). It is clear that there are neurocognitive disorders that have both neurotoxic and neuroadaptive mechanisms involved, and the lines between these two categories can quickly start to blur. As an example, lack of proper insight (anosognosia) and metacognition about one’s own substance use disorder may be considered either a cognitive maladaptation relating to a preference to sustain drug use or neuropsychological deficits caused by neurotoxic effects.

Regardless of cause, these symptoms can lead users to deny addiction as a health problem and reduce motivation to seek or accept treatment (H. Ekhtiari, Rezapour, Aupperle, & Paulus, 2017). Thus, CDs and CMs associated with drug use would potentially benefit more from integrating different cognitive-based interventions (cognitive modifications and cognitive rehabilitations) into a holistic program rather than employing each separately. Drug users could also benefit from structured psychoeducation (PE) programs aiming to transfer knowledge about different aspects of addiction and increase insight and motivation for recovery. The following sections provide more detailed description for these interventions.

2.1. Neuroscience-informed Psychoeducation and Metacognitive Training

The ability to reflect about and regulate one's internal world of thoughts, feelings and mental processes is termed "metacognition" (Flavell, 1979; Roebbers, 2017; Sadeghi, Ekhtiari, Bahrami, & Ahmadabadi, 2017). Distortion of this higher order function is apparent in the observation that people with SUDs often underestimate or inaccurately report on their symptoms (Inchausti, Ortuño-Sierra, García-Poveda, & Ballesteros-Prados, 2016; Moeller et al., 2016; Verdejo-Garcia, Clark, & Dunn, 2012). These deficits are thought to potentially arise due to damages in neural networks that include the anterior cingulate cortex and insula (Fleming, Huijgen, & Dolan, 2012). Poor metacognitive functions relate to reduced consistency between subjective symptoms and real objective states (e.g. self-report craving and actual arousal states) (Castine et al., 2018), denial of problems associated with drug use (Moeller & Goldstein, 2014) and decreased interoceptive sensations or awareness (Ateş Col, Sonmez, & Vardar, 2016). A recent study in cocaine users reported an association between metacognition impairment and poor treatment outcome due to reduced treatment motivation (Castine et al., 2018). These evidences suggest a need to embed interventions that directly target metacognition into the context of addiction medicine. Accordingly, there are different interventions that may enhance metacognition for SU. This includes motivational interviewing, which could enhance metacognition through the enhancement of insight and motivation for change (Apodaca & Longabaugh, 2009), as well as psychoeducation programs aiming to improve subject's awareness about their own mental health disorder and related problems (H. Ekhtiari et al., 2017). Improved insight may change negative attitudes to recovery and reduce potential stigma that is an important impediment to addiction treatment (Hasan et al., 2015). Moreover, training patients to use self-assessment and self-monitoring in daily life activities in order to identify their symptoms or problems (e.g., difficulty in shifting attention or immediate forgetting new information) would be a promising therapeutic intervention in this context (Skidmore, Swafford, Juengst, & Terhorst, 2018). Other strategies that enhance awareness of one's internal bodily states or processes and the external world (i.e., mindfulness), could also be promising for enhancing insight and metacognition (Shapiro, Carlson, Astin, & Freedman, 2006). Common to all these approaches is a core focus on supporting the integration of both internal and external relevant cues to create a self-representation that is close to the true state.

2.2. Neuroscience Informed Cognitive Modifications

Having a conceptual framework that provides specific targets for neuroscience-informed interventions is critical. The dynamic craving model (DCM) as depicted in figure 1 can be

considered a potential framework to define targets and categorize interventions as well as for providing guidance in measuring the efficacy of such interventions (H. Ekhtiari, Nasser, Yavari, Mokri, & Monterosso, 2016). The traditional cognitive behavioral therapy (CBT)-based model (Beck, 1997) adapted for drug craving, that is often used to guide relapse prevention packages, involves four main elements: triggers, thoughts/affect, craving and drug use (Larimer, Palmer, & Marlatt, 1999; Oei, Lim, & Young, 1991). In the DCM, thoughts and craving are delineated into 5 major cognitive processes, namely, attention, saliency valuation, memory, interoception and executive control modules. Each of these modules have sub processes, reflected to some extent in the top/bottom of each cell of figure 1. As it has been indicated in the model, exposure to the environmental stimuli (E) (including both internal and

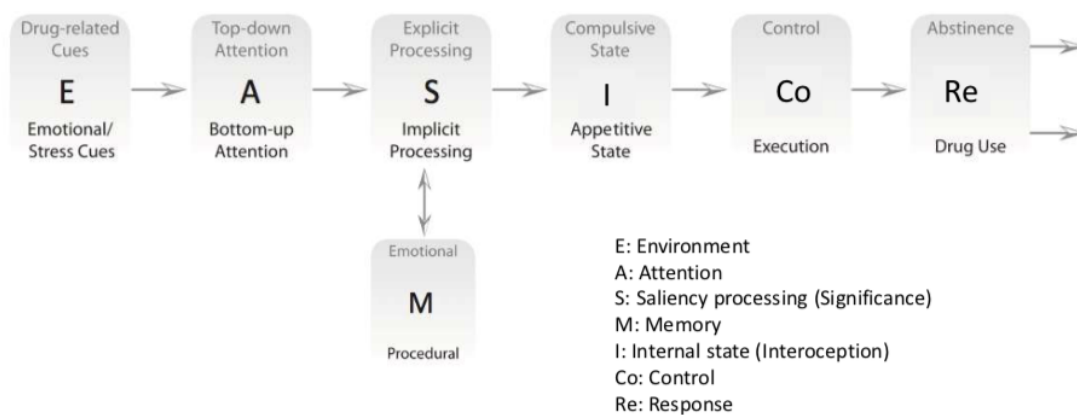


Figure 1. Dynamic model of craving (DCM). A neuroscience informed conceptual framework to define the major targets in the dynamic response to drug related or emotional salient cues.

external cues) activates the process of drug craving. These cues then elicit distinct yet collaborative bottom-up and top-down attentional processes that increase the focus of attention on drug-relevant cues (A). This attentional deployment activates saliency evaluation processes (S) related to drug-associated cues. The retrieval of memories (M) linked to the drug cues provides relevant information during saliency processing. Saliency evaluation can result in an interoceptive state that represents the subjective feeling of craving, leading to the engagement of executive control (Co) processes to take execute actions supporting drug-taking behavior or abstinence (Response) (H. Ekhtiari et al., 2016). Below, we will further discuss these 5 modules and cognitive interventions that may target each.

2.2.1. Attention bias interventions

The unconscious orientation of attention towards substance related cues is termed “attentional bias” and is considered among the most prominent cognitive maladaptive changes in chronic drug/alcohol users (Cox, Fadardi, Intriligator, & Klinger, 2014). Attentional bias is thought to result from an increase in the brain’s automatic attentional processes and a decrease in the reflective ones (Stacy & Wiers, 2010). Attentional bias has been considered as a potential “early warning signal”, as it seems to occur automatically when substance users are exposed to drug related cues and can lead to relapse for subjects with SUDs who are undergoing treatment (Field, Marhe, & Franken, 2014). In fact, recent findings suggest

that substance users who have greater attentional bias towards drug-related cues (measured by modified Stroop tasks) are more likely to drop out from the treatment, have shorter length of stay in treatment, and have greater subsequent drug consumption (Diaz-Batanero, Dominguez-Salas, Moraleda, Fernandez-Calderon, & Lozano, 2018; Streeter et al., 2008). In this context, a series of interventions has been applied to retrain biases away from substance-related cues towards more neutral ones in the environment. These computer-based interventions, referred to as Attention Bias Modification (ABM), are based on the well-known visual dot probe implicit association tasks. In brief, one drug-related and one neutral stimulus are shown on the screen simultaneously, after which a “probe” target stimulus (i.e., an X) is displayed in the location of one of the stimuli. For ABM, the probe is shown in the location of the neutral stimuli with a higher probability (e.g., 80%), thus training participants to disengage their attention from drug-related stimuli and shift it towards the paired neutral ones (Cristea, Kok, & Cuijpers, 2016; Heitmann, Bennis, van Hemel-Ruiter, & de Jong, 2018).

2.2.2. Saliency-based interventions

The ability to properly attenuate, amplify and maintain an emotional response is termed as Emotional Regulation (ER) (Axelrod, Perepletchikova, Holtzman, & Sinha, 2011). Among ER strategies, cognitive reappraisal (CR) has received particular attention in the field of drug addiction. By using CR strategies, patients learn how to re-evaluate and reinterpret emotional experiences in order to alter the meaning given to them and potentially reduce the saliency of affect experienced (Steinberger, Payne, & Kensinger, 2011). CR is critical for managing emotional situations and responses to emotionally-salient cues. Hence, impairments in CR could lead to improper behavioral actions (e.g., avoidance or appetitive reaction) due to misinterpretation or decreased tolerance of an emotional experience (Pietrek, Popov, Steffen, Miller, & Rockstroh, 2012). CR strategies for saliency modification in negative affect (i.e., anxiety, depression) have been adapted in attempts to target appetitive response to drug-related salient cues for the purposes of craving management and relapse prevention. It has also been well established that people with SUDs have different degrees of ER impairments that may contribute to increased cue-induced craving and poor treatment response (Berking et al., 2011; Daughters et al., 2005; Hopwood, Schade, Matusiewicz, Daughters, & Lejuez, 2015; Strong, 2012; Wilcox, Pommy, & Adinoff, 2016). Hence, embedding CR could provide added value to standard treatments. CR can be used to target cognitions concerning drug use and feelings of craving, or it can be used to target affective states or stress that may serve as cues or triggers for subsequent use. Although there is a plethora of studies supporting the use of cognitive therapy for conditions often comorbid with substance use (e.g., anxiety, mood, and trauma-related disorders) (Butler, Chapman, Forman, & Beck, 2006), there is less evidence supporting the efficacy of CR for targeting substance use specifically. One study among cigarette users suggests that CR may be associated with weaker expectancies that smoking alleviates negative feelings and induces positive mood (Fucito, Juliano, & Toll, 2010). Moreover, based on the previous findings on ER, it should be noted that the successful implementation of saliency modification strategies may directly depend upon patients' awareness of their emotions and internal bodily states (i.e., urges, cravings) as well as their capacity to control their behaviors (Hopwood et al., 2015). Interoceptive awareness and self-control will be discussed in more detail in subsequent sections of this chapter.

Contingency management (CM) is one of the most efficacious treatments for substance use and could be viewed as targeting saliency processing. CM attempts to combat the saliency and reward of drug use or cues with rewards that are contingent upon abstinence and incompatible with drug use (e.g., a prize or voucher) (Potenza, Sofuoglu, Carroll, & Rounsaville, 2011; Stanger, Budney, & Bickel, 2013). CM takes advantage of the fact that the brain processes immediate rewards as more salient and motivating than longer-term rewards, providing a briefer immediate reward (voucher or prize) for continued abstinence (Kiluk & Carroll, 2013).

2.2.3. Memory-based interventions

Repeated pairing of drug related cues (e.g., sight of a syringe) with rewarding outcomes (hedonic state) forms a type of learning (instrumental/operant) whereby the cue becomes the reward anticipator (salient stimulus) that can trigger drug-seeking and-taking behaviors (Hogarth, Balleine, Corbit, & Killcross, 2013). One prominent neural change in response to such drug-related operant cues is increased dopamine release, which is linked to increased emotional arousal (e.g., increased heart rate) as well as learning and memory consolidation about the drug related cue. Re-exposure to these cues and retrieval of related emotional memories (via hippocampal/amygdala connections to various brain structures/networks), promotes craving followed by relapsing behaviors (Torregrossa, Corlett, & Taylor, 2011; Torregrossa & Taylor, 2013). Hence, the interventions that modulate encoding and retrieval of emotional-motivational memories could attenuate the intensity of both positive and negative affective-appetitive states (Sorg, 2012). Recent studies have begun to examine the potential benefit of treatments aimed at reshaping addiction memories in the process of selective retrieval and targeted reconsolidation (Liddie & Itzhak, 2016; Sorg, 2012). According to the memory reconsolidation hypothesis, previous memories become pliable and susceptible to disruption immediately after they are retrieved (Shi et al., 2015). Thus, during active retrieval, it may be possible to modify or alter the affective salience of memories by incorporating new and somehow interfering information (Lee, Nader, & Schiller, 2017; Torregrossa & Taylor, 2013). For example, when a drug-related memory is reactivated by the presence of a drug-related cue, a patient could potentially add or modify this memory with new information (e.g., imagining the negative outcomes for the drug use, considering what would have happened if they would have abstained and went home to their family instead, etc.) preferentially in a controlled environment and with the guidance of a therapist. Doing so could diminish the salient value of the initial memory. Another strategy during reconsolidation is to broaden the “memory tunnel” by orienting their attention towards more peripheral details (e.g., spatial and temporal details) of the memory rather than only focusing on their emotional aspects (Rimmele, Davachi, Petrov, Dougal, & Phelps, 2011). These types of memory trade-offs (between new and old, emotional and non-emotional, could deliberately interfere with memory processes to suppress cue-induced craving.

In addition to reconsolidation and extension of retrospective memories, patients with SUDs may also benefit from strategies modulating prospective memory. Episodic future thinking

(EFT) is defined as the ability to mentally travel in time and vividly pre-experience future events (Snider, LaConte, & Bickel, 2016). EFT has been shown to modify delay discounting behaviors, purportedly through expanding the temporal window in which individuals are considering consequences of their decisions (Bromberg, Wiehler, & Peters, 2015). EFT has been shown to be effective in reducing delay discounting and demand rate in alcohol users (Bulley & Gullo, 2017; Snider et al., 2018; Snider et al., 2016). EFT strategies could also theoretically be helpful in targeting the planning and prospective memory neuropsychological deficits documented in SUDs (Heffernan, 2008; Rendell, Mazur, & Henry, 2009).

2.2.4. Interoceptive-based interventions

When we come across an emotional/appetitive stimulus or cue (either internal or external), interoception helps us to accurately receive, process and integrate different body-relevant signals originating from our visceral organs (e.g., heart, stomach) to inform decision-making (Paulus, Stewart, & Haase, 2013; Stewart, May, Tapert, & Paulus, 2015). In healthy subjects, afferent neural signals about interoceptive changes (e.g., increased heart rate) serve as warnings about sub-optimal conditions (e.g., being in danger) and prompt approach or avoidance behavior to respond appropriately to the danger and return the body to an equilibrium state. This communication flows between peripheral receptors, c-fiber afferents, spino-thalamic projections, specific thalamic nuclei, posterior and anterior insula, and anterior cingulate cortex (ACC) (Paulus et al., 2013). There has been consistent evidence concerning disrupted interoceptive awareness (IA) in drug users (Berk et al., 2015). Specifically, it has been proposed that drug users develop increased or decreased IA to different salient stimuli following chronic drug use (Ates Col et al., 2016; Verdejo-Garcia et al., 2012). In the case of decreased IA, subjects may become less aware of aversive bodily signals evoked in response to drug related cues. In the case of increased IA, subjects may become hyper-aware of their bodily states but do not interpret them accurately. Instead, any visceral changes (e.g., increased heart rate) experienced might be perceived as either a symptom of withdrawal or distress, thereby triggering substance use to alleviate this negative affective state with positive emotions (e.g., relief, pleasure). This repeated pattern further embeds the negative reinforcement properties of substance use (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004). The discrepancy between the person's ideal state (experienced during drug use) and the actual one (experienced during states of craving or distress) are thought to generate body-prediction error signals. Interventions suggested to be potentially effective in modulating interoceptive processes for drug users include mindfulness and physical exercise (Paulus et al., 2013). In mindfulness-based exercises, participants are trained to focus attention on their bodily states in the present moment without judging them (Price & Hooven, 2018). There has been some initial evidence of efficacy for mindfulness interventions with alcohol and drug use (Witkiewitz, Lustyk, & Bowen, 2013; Zgierska et al., 2008). With physical exercise, subjects learn how to adjust their exertion based on feed-forward (expectations) and feedback (body-relevant sensing) information (Paulus et al., 2013). Although there is lack of evidence for the neural mechanisms that underlie the beneficial effects of physical exercise on drug-taking behavior in substance users (Rawson et al., 2015; Robertson et al., 2016), it is hypothesized that repeated engagement in controlled, interoceptive goal-action (exercise)

could enhance functioning of interoceptive-related networks (i.e., insula, ACC) and help patients be more prepared to interpret and respond to body relevant information triggered by drug-related stimuli (Paulus et al., 2013).

2.2.5. Inhibitory control interventions

Substance and alcohol use have consistently been associated with deficits in cognitive control and response inhibition, including tendencies to act prematurely and impulsively. This includes engaging automatically in drug-related habitual behaviors despite negative consequences for the behavior (Sherman, Baker, Squeglia, & McRae-Clark, 2018). Cognitive control is likely impacted by many different neurocognitive processes, including attentional biases or dysregulation, memory processes, salience of cues and outcomes, or misinterpretation of interoceptive signals. Thus, many of the interventions discussed above could potentially impact cognitive control abilities as well. However, there are also interventions that more specifically target cognitive control. Many interventions aim to decrease automatic, habitual drug-use behaviors by enhancing self-awareness of these behaviors and their cues, and the forming of new habits (Cleo, Glasziou, Beller, Isenring, & Thomas, 2018). This is usually accomplished via self-monitoring (e.g., of cues, emotions, behaviors), identifying alternative behaviors to drug use, planning and goal-setting, and reviewing progress (Kliemann et al., 2017; McGowan, 2013). One such strategy for enhancing planning and problem-solving is goal management training (Alfonso, Caracul, Delgado-Pastor, & Verdejo-Garcia, 2011). Realistic expectations and patient motivation are crucial for successful implementation of these interventions (Gardner, Lally, & Wardle, 2012).

Approach bias modification (ApBM) is a more recently investigated approach for modifying automatic behaviors to drug-related cues. These are similar to ABMs in that they are computer-based training of responses to drug-related stimuli, but while ABMs focus on training visual attention to drug-related versus neutral cues, ApBMs focus on training behavioral approach-avoidance responses to drug-related cues. (Cousijn, Goudriaan, & Wiers, 2011; C. E. Wiers et al., 2014). One of the most well-known ApBM means is the approach-avoidance paradigm in which different pictures (including neutral and drug-related cues) are shown to subjects on computer screen (R.W. Wiers et al., 2015). Participants are asked to respond to a stimulus-feature unrelated to the contents of the picture (landscape/portrait format, left/right rotation) by pulling or pushing the joystick (Eberl et al., 2013). By pushing the joystick (resembling avoidance action) the picture size decreases while by pulling it (resembling approach action) the picture size increases (Neumann & Strack, 2000). By having the subject disproportionately engage in avoidance actions in response to drug cues (e.g., 80% of trials), it is thought that this may modify the individual's automatic responses to drug cues in their daily life. Although the ApBM is a novel approach in the field of addiction treatment, there are a few studies suggesting it may have promise for decreasing relapse rates (Eberl et al., 2013; R. W. Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011), subjective craving (R.W. Wiers et al., 2015), as well as neural activity in brain regions involved in reward processing of drug related stimuli (e.g., medial prefrontal cortex and nucleus accumbens) in alcohol (C. E. Wiers et al., 2014) and cannabis users (Cousijn et al., 2012) (More details on ApBM in chapter 17). In addition to ApBM, repeated practice with inhibitory control

paradigms such as go/no go or stroop-related tasks, may increase one's ability to withhold prepotent responses in order to engage in more goal-directed behaviors (Houben, Havermans, Nederkoorn, & Jansen, 2012). These types of training paradigms have been successful in experimental settings for reducing implicit attitudes and alcohol intake acutely, though the pragmatic application and efficacy in real clinical settings needs further investigation (Bowley et al., 2013; Houben et al., 2012). You can find more details on inhibitory control training in chapter 19.

2.3. Neurocognitive Rehabilitation

As mentioned above, individuals with SUDs suffer from various deficits in more general neuropsychological functions, including flexibility, visuospatial skills, psychomotor speed, attention, concentration, verbal fluency, reasoning, problem solving and episodic memory (Rezapour, DeVito, Sofuoglu, & Ekhtiari, 2016). These impairments can interfere with treatment by reducing the ability of a user to receive, encode, integrate, and employ therapeutic strategies, both in the context of treatment sessions and in their everyday lives (Rezapour et al., 2016). Therefore, SUDs could potentially benefit from therapeutic interventions similar to cognitive rehabilitation programs for other populations (e.g., traumatic brain injury, severe mental illness), which support compensatory and/or restorative strategies. These types of interventions have been successfully employed for stimulant, opiate and alcohol users (Bell, Vissicchio, & Weinstein, 2016; Bickel, Yi, Landes, Hill, & Baxter, 2011; Gamito et al., 2014; Goldstein, Haas, Shemansky, Barnett, & Salmon-Cox, 2005; Marceau, Berry, Lunn, Kelly, & Solowij, 2017; Rass et al., 2015; Rezapour, Hatami, et al., 2017b; Rupp, Kemmler, Kurz, Hinterhuber, & Fleischhacker, 2012; Snider et al., 2018; Wanmaker et al., 2018; Zhu et al., 2018). The finding from these studies show initial promise that cognitive rehabilitation programs may enhance cognitive function and increase efficacy of broader SUD treatment programs (Bates, Buckman, & Nguyen, 2013). However, this research has primarily relied upon small samples and there has been a relative lack of replication outside the development team or to real-world clinical settings. Thus, there remains much work to be done for these interventions to be more broadly adopted into the daily practice of addiction medicine.

To summarize, the DCM model (figure 1) provides a neuroscience-informed way of conceptualizing different cognitive components that can potentially be targeted in substance use treatment. The most robust clinical effects could potentially be supported through integration of both cognitive modification and rehabilitation strategies that target different aspects of the DCM model. Ideally, such a model could eventually be used to identify areas of strengths and weaknesses for each individual and inform customized treatments to meet individual patients' needs. In the following section, we will discuss an example program that attempts to integrate different cognitive education, modification, and rehabilitation strategies into a program that targets various aspects of the DCM model.

3. Integrative Cognitive interventions: Introducing NEAT program

Based on research concerning the various cognitive maladaptive responses and deficits associated with SUD and the various strategies that have shown potential for targeting

aspects of the DCM model, we have developed a new program titled “Neurocognitive Empowerment for Addiction Treatment (NEAT)”. NEAT incorporates psychoeducation, cognitive rehabilitation, and modification strategies with materials that are specifically designed to be relevant for SUDs and thus, increase the potential for transference of training effects to daily functioning and treatment outcome. As a neuroscience-based program, NEAT (as well as the DCM model) was developed in the spirit of the Research Domain Criteria (RDoC) model, provided by National Institute of Mental Health (Insel et al., 2010). RDoC supports the examination of dimensions of function rather than discrete categorical definitions (i.e., diagnoses). NEAT was developed with the idea of targeting various domains of functioning, including the RDoC domains of cognitive systems (e.g., attention, executive control, and working memory), positive/negative valence processing (e.g., reward/threat processing), and arousal/modulatory systems (e.g., sleep-wake cycles, alertness).

In terms of content, the NEAT program is organized into five main parts as follows:

Part 1: Brain Education: The main purpose of these components is to promote patient’s awareness about the cognitive impairments often associated with drug addiction. Patients are provided with information concerning common behavioral manifestation of these impairments in daily life activities. They are informed about lifestyle changes (e.g., nutrition, physical exercise) that can facilitate brain recovery. To improve learning and consolidation, the education components are accompanied by colorful and comic cartoons (H. Ekhtiari et al., 2017). Figure 2 illustrates a sample of used cartoons.

Part 2: Compensatory strategies: The main purpose of these components is to provide specific cognitive strategies for supporting optimal cognitive function or compensating for deficits. For example, providing strategies and practice for expanding tunnel memory for drug-related or emotional memories or mnemonic aids and goal management training for memory- and planning-related problems. These components are integrated with the brain exercises discussed next in order to illustrate and practice each cognitive function and compensatory strategy.

Part3: Brain exercises: According to our previous experiences in another cognitive rehabilitation package named NECOREDA (NEuroCOgnitive REhabilitation for Disease of Addiction) (Rezapour et al., 2015), using brain exercises with different gradients of game-based features could be useful for restoration of brain functions among people with SUDs. These game-based exercises include such things as Stroop-like tasks, mazes, target cancellation tasks, and so on. In NEAT, these games are used not only as a potential way of practicing and improving specific brain functions but also for providing a foundation for discussions to enhance metacognition (the next component).



Figure 2. Cartoon development pipeline for the Neurocognitive Empowerment for Addiction Treatment (NEAT) package starting from character development and selection (panel A), ideas development (panel B) and finalized cartoons depicting cognitive deficits in SUDs including attentional bias, memory, and executive control (panel C) (Cartoons by Naeem Tadayon and Joshua Donbar, courtesy of Laureate Institute for Brain Research).

Part 4: Metacognitive training: Metacognition awareness is trained in this program by providing information about the cognitive functions engaged in each brain exercise and the role that these functions (and the associated compensatory strategies) play in their day to day functioning and substance use recovery. This part targets insight towards the cognitive foundations of the training program and aims to enhance motivation to implement skills and generalization of learning.

Part 5: Brain planner: Training patients to keep records of their daily activities, including both retrospective (e.g., past events) and prospective forms (e.g., future goals), is another critical aspect of NEAT. This supports higher-order cognitive functions such as self-monitoring and planning (which are trained within compensatory strategies) as well as basic cognitive functions including memory and episodic future thinking in the context of daily life activities. The use of a planner also supports compliance with NEAT and other SU treatment activities. Each training session of NEAT has time dedicated to learning and practicing using the planner.

As a paper-based training program, NEAT has 14 sessions that include both in-session materials and homework. The sessions are presented in an additive structure in which basic cognitive functions (i.e., attention, working memory) are presented prior to higher order cognitive functions (i.e., inhibition, planning, prospective memory). New concepts and skills are added gradually throughout the sessions. Figure 3 shows the architecture of the 14 sessions of NEAT.

4. Other neuroscience-informed interventions

In addition to the interventions that have been addressed earlier in this chapter, there are other groups of interventions that may target neuroscience-informed biomarkers. For example, administration of atomoxetine and propranolol has been shown to reduce attentional biases and affect drug related memories in cocaine and heroin users, respectively (Passamonti et al., 2017; Zhao et al., 2011) and brain stimulation or neurofeedback techniques may be used to target neural networks more directly (Yavari et al., 2016). Many of these are covered in previous chapters of this book. Ideally, cognitive-based interventions discussed herein would be integrated with these other types of interventions in a holistic and personalized medicine approach to optimize treatment for individual patients.

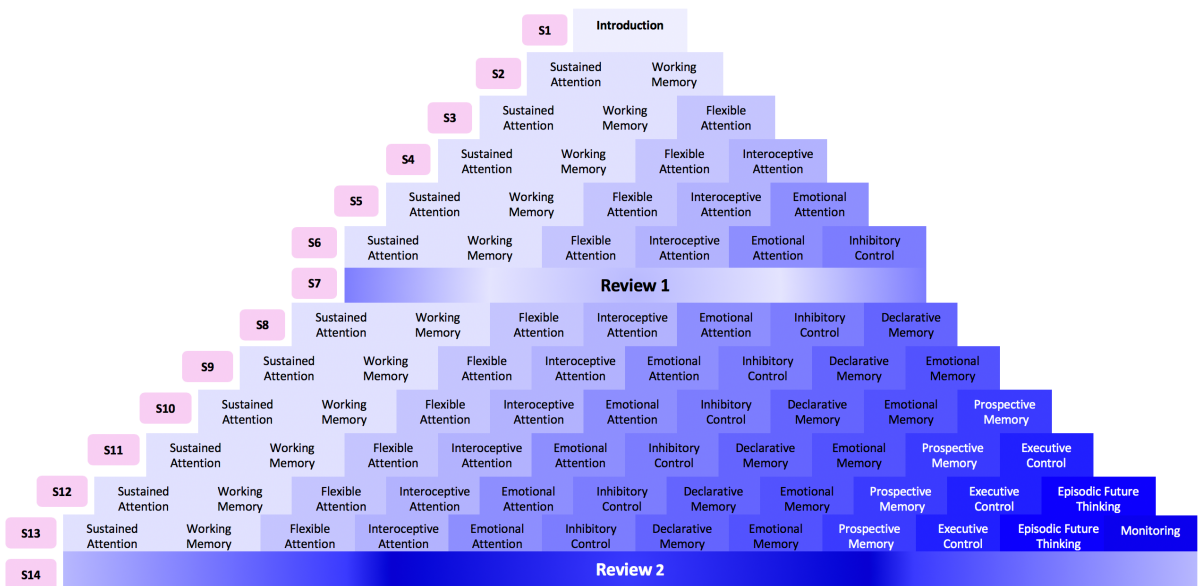


Figure 3. Architecture of Neurocognitive Empowerment for Addiction Treatment (NEAT) for 14 sessions

5. Future Directions:

In the more advanced fields of medicine, like cardiology or oncology, patients are assessed based on quantitative biomarkers that are reliable and reflecting disease pathogenesis. Then, the most effective treatment for the individual are selected or even personally designed based on the biomarker profile. Furthermore, the efficacy of these individualized interventions is monitored with these same or new biomarkers in order to assess long term trajectory of recovery. Currently, this seems like a dream in psychiatry in general and addiction medicine in particular. However, recent advances in human brain mapping, genome analysis, blood biochemistry and continuous peripheral physiological recording (e.g., heart rate variability, sleep/awake behavior and skin conductance response), combined with the development of novel cognitive interventions that may target many of these biomarkers, provides hope for the future of neuroscience-informed addiction treatment.

In the ideal scenario, neuroscience-based interventions in addiction medicine should address following four features. Here, we have also provided ideas based on our new trials for the NEAT package on how these features could be met in the development of a neuroscience-informed cognitive intervention.

- 1. Targets a specific neuroscience-based mechanism or set of mechanisms informed by previous studies.** DCM model as a neuroscience-informed modular model provides core mechanisms that NEAT targets (e.g., attention, salience, interoception, memory, and cognitive control processing and the associated prefrontal-limbic networks).
- 2. Has a neuroscience-based biomarker based on the targeted mechanism/s to predict response to treatment or to help with treatment selection.** In the development of NEAT, we are utilizing baseline and post-treatment fMRI assessments of neural reactivity during cue reactivity, interoception, and response inhibition. This will allow us to potentially identify and validate fMRI biomarkers for prediction and/or monitoring.
- 3. Has a neuroscience-based biomarker based on the targeted mechanism as an outcome measure to monitor the efficacy of intervention over time.** Considering fMRI outcome measures along with clinical outcome measures in our ongoing NEAT trials allows us to assess mechanistic target engagement.
- 4. Has the potential to be optimized or modified based on observed values of the targeted neuroscience-based biomarker.** Based on the self-report, cognitive, and fMRI assessments included in our initial trials, the hope would be that eventually these same assessments could be used to inform the personalization of NEAT. Participants could be providing feedback based on pre-treatment, multi-level assessments that could be used to motivate their treatment engagement and point to specific domains of function to be addressed.

While advancements in biomarkers and interventions continue, we need to continually be aware of how we can bridge the gap between laboratory research and clinical implementation. Such translation can only be accomplished through pragmatic clinical trials that test effects identified in experimental settings on a larger scale. We should not forget that even in the ideal scenarios we referred to in cardiology and oncology, it takes years to translate from initial basic laboratory findings to clinical efficacy, and finally to treatment effectiveness in real-world settings. Thus, neuroscience-informed cognitive interventions are unlikely to be a quick silver bullet cure for addiction. However, with continual translation between neuroscience, controlled laboratory settings, and real-world clinical implementation, we will hopefully continue to significantly improve the landscape of treatment options for individuals suffering from substance use.

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